

What is claimed:

1. A method for identifying inhibitors of protein kinases comprising:
providing a first module having a one or more functional groups for binding to
catalytic residues of the protein kinase;
combining the first module with a second module which provides a non-
peptide scaffold; and
selecting combinations of the first and second modules which inhibit protein
kinase activity.

2. The method according to claim 1, wherein said providing a first
module comprises:
attaching the first module to a peptide scaffold;
identifying one or more functional groups which preferentially bind to
catalytic residues of the protein kinase; and wherein said combining the first module
with the second module comprises:
substituting the second module for the peptide scaffold.

3. The method according to claim 1, wherein the first module comprises a
functional group selected from the group consisting of boronic acid, a hydroxyl group,
phosphonic acid, sulfamic acid, a guanidino group, carboxylic acid, an aldehyde, an
amide, and hydroxymethylphosphonic acid.

4. The method according to claim 3, wherein the first module comprises
two or more functional groups.

5. The method according to claim 3, wherein the first module comprises a
boronic acid group.

6. The method according to claim 3, wherein the first module comprises a
hydroxyl group.

7. The method according to claim 3, wherein the first module comprises a
amide group.

8. The method according to claim 7, wherein the amide group is a vicinal
5 tricarbonyl amide.

9. The method according to claim 1, wherein the second module
comprises a group selected from the group consisting of indole, naphthalene,
biphenyl, isoquinoline, benzofuran, and benzothiophene.

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10. The method according to claim 9, wherein the second module
comprises an indole.

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11. The method according to claim 9, wherein the second module
comprises naphthalene.

12. The method according to claim 1, wherein more than one first module
is bound to the second module.

13. The method according to claim 1, wherein the first module further
comprises a linear chain comprising between one and three carbon atoms which links
the first module to the second module.

14. The method according to claim 13, wherein one of the carbon atoms in
25 the linear chain is substituted with a nitrogen, oxygen or sulfur atom.

15. The method according to claim 1, wherein the protein kinase is a
protein tyrosine kinase.

30 16. The method according to claim 15, wherein the protein tyrosine kinase
is selected from the group consisting of pp60^{c-src}, p56^{lck}, ZAP kinase, platelet derived
growth factor receptor tyrosine kinase, Bcr-Abl, VEGF receptor tyrosine kinase, and

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is pp60^{c-src}.

18. The method according to claim 1, wherein the protein kinase is a protein serine kinase.

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23. *Testing*
A method

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comparing the level of protein kinase activity to the level of activity from the protein kinase without the presence of the inhibitor.

24. A method of inhibiting a protein kinase comprising: *reagent compound*
5 contacting the protein kinase with a compound comprising a first module having a functionality for binding to catalytic residues of the protein kinase and a second module which provides a non-peptide scaffold, wherein the combination of the first and second modules inhibits the protein kinase's activity.

10 25. The method according to claim 24, wherein the first module comprises a functional group selected from the group consisting of boronic acid, hydroxy, phosphonic acid, sulfamic acid, a guanidino group, carboxylic acid, an aldehyde, an amide, and hydroxymethylphosphonic acid.

15 26. The method according to claim 25, wherein the first module comprises a boronic acid group.

20 27. The method according to claim 25, wherein the first module comprises a hydroxyl group

28. The method according to claim 24, wherein the second module comprises a group selected from the group consisting of indole, naphthalene, biphenyl, isoquinoline, benzofuran, and benzothiophene.

25 29. The method according to claim 28, wherein the second module comprises an indole.

30 30. The method according to claim 28, wherein the second module comprises naphthalene.

31. The method according to claim 24, wherein more than one first module is bound to the second module.

32. The method according to claim 24, wherein a linear chain comprising between one and three carbon atoms links the first module to the second module.

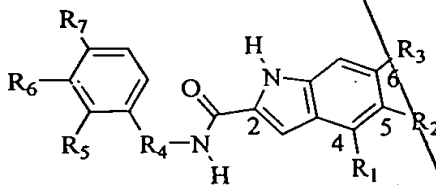
33. The method according to claim 32, wherein one of the carbon atoms in the linear chain is substituted with a nitrogen, oxygen or sulfur atom.

34. The method according to claim 24, wherein the protein kinase is a protein tyrosine kinase.

35. The method according to claim 34, wherein the protein tyrosine kinase is selected from the group consisting of pp60^{c-src}, p56^{lck}, ZAP kinase, platelet derived growth factor receptor tyrosine kinase, Bcr-Abl, VEGF receptor tyrosine kinase, and epidermal growth factor receptor tyrosine kinase and epidermal growth factor receptor-like tyrosine kinases.

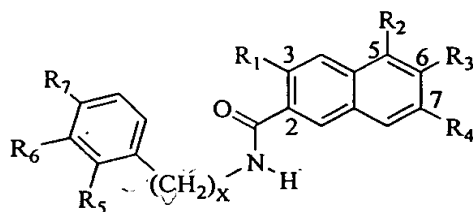
36. The method according to claim 34, wherein the protein tyrosine kinase is pp60^{c-src}.

37. The method according to claim 34, wherein the compound has the following formula:



wherein R1 is H or OH, R2 is H or OH, R3 is OH or H, and R4 is CH₃, CH₂(CH₃)R, or CH₂(CH₃)S, R5 is OCH₃, H, or OH, R6 is OCH₃, F, H, or OH, and R7 is OCH₃, H, OH, CO₂H, CO₂CH₃, CH₂CO₂H, or CH₂CO₂CH₃.

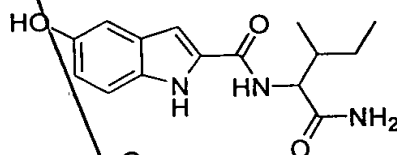
38. The method according to claim 34, wherein the compound has the following formula:



5 wherein R1 is OH or H, R2 is OH or H, R3 is OH or H, R4 is OH or H, R5 is OH, OMe, or H, R6 is OH, OMe, or H, R7 is OH, OMe, or H, and X is 0 or 1.

39. The method according to claim 34, wherein the compound has a specificity group which is an aliphatic amide.

40. The method according to claim 39, wherein the compound has the following structure:

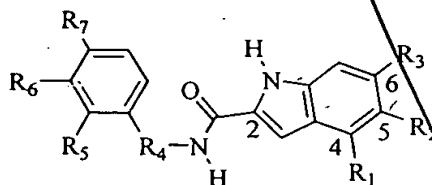


41. The method according to claim 24, wherein the protein kinase is a protein serine kinase.

42. The method according to claim 41, wherein the protein serine kinase is selected from the group consisting of MAP kinase, protein kinase C, and CDK kinase.

43. The method according to claim 24, wherein the compound further comprises one or more specificity side chain elements attached to the combination of the first and second modules.

44. A non-peptide protein tyrosine kinase inhibitor having the formula:



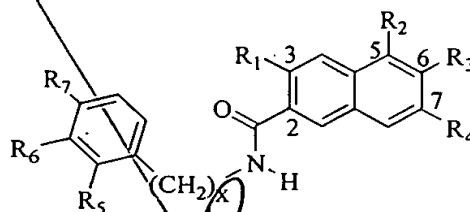
wherein R1 is H or OH, R2 is H or OH, R3 is OH or H, and R4 is CH₃, CH₂(CH₃)R, or CH₂(CH₃)S, R5 is OCH₃, H, or OH, R6 is OCH₃, F, H, or OH, and R7 is OCH₃, H, OH, CO₂H, CO₂CH₃, CH₂CO₂H, or CH₂CO₂CH₃.

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45. The non-peptide protein tyrosine kinase inhibitor according to claim 44, wherein the non-peptide protein tyrosine kinase inhibitor inhibits the activity of pp60^{c-src} tyrosine kinase.

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46. A non-peptide protein tyrosine kinase inhibitor having the formula:



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wherein R1 is OH or H, R2 is OH or H, R3 is OH or H, R4 is OH or H, R5 is OH, OMe, or H, R6 is OH, OMe, or H, R7 is OH, OMe, or H, and X is 0 or 1.

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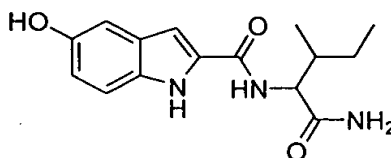
47. The non-peptide protein tyrosine kinase inhibitor according to claim 46, wherein R1 is OH, R2 is OH, R3 is H, R4 is H, R5 is OMe, R6 is H, R7 is H, and X is 1.

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48. The non-peptide protein tyrosine kinase inhibitor according to claim 46, wherein the non-peptide protein tyrosine kinase inhibitor inhibits the activity of pp60^{c-src} tyrosine kinase.

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49. A non-peptide protein tyrosine kinase inhibitor having the formula:



50. A method of treating a condition, responsive to a protein kinase inhibitor, in a patient comprising:

administering an effective dose of a protein kinase inhibitor to a patient wherein the protein kinase inhibitor comprises a first module having a functionality for binding to catalytic residues of the protein kinase and a second module which provides a non-peptide scaffold, wherein the combination of the first and second modules inhibits protein kinase activity.

51. The method according to claim 50, wherein the condition is selected from the group consisting of cancer, psoriasis, arthrosclerosis, or immune system activity.

52. The method according to claim 50, wherein the first module comprises a functional group selected from the group consisting of boronic acid, hydroxy, phosphonic acid, sulfamic acid, a guanidino group, carboxylic acid, an aldehyde, an amide, and hydroxymethylphosphonic acid.

53. The method according to claim 52, wherein the first module comprises a boronic acid group.

54. The method according to claim 52, wherein the first module comprises a hydroxyl group

55. The method according to claim 50, wherein the second module comprises a group selected from the group consisting of indole, naphthalene, biphenyl, isoquinoline, benzofuran, and benzothiophene.

56. The method according to claim 55, wherein the second module comprises indole.

57. The method according to claim 55, wherein the second module comprises naphthalene.

58. The method according to claim 50, wherein more than one first module is bound to the second module.

59. The method according to claim 50, wherein a linear chain comprising between one and three carbon atoms links the first module to the second module.

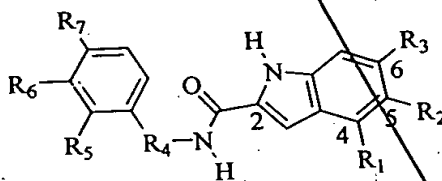
60. The method according to claim 59, wherein one of the carbon atoms in the linear chain is substituted with a nitrogen, oxygen or sulfur atom.

61. The method according to claim 50, wherein the protein kinase is a protein tyrosine kinase.

62. The method according to claim 61, wherein the protein tyrosine kinase is selected from the group consisting of pp60^{c-src}, p56^{lck}, ZAP kinase, platelet derived growth factor receptor tyrosine kinase, Bcr-Abl, VEGF receptor tyrosine kinase, and epidermal growth factor receptor tyrosine kinase, and epidermal growth factor receptor-like tyrosine kinases.

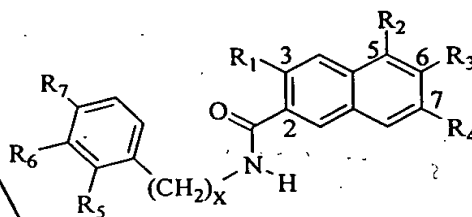
63. The method according to claim 62, wherein the protein tyrosine kinase is pp60^{c-src}.

64. The method according to claim 63, wherein the compound has the following formula:



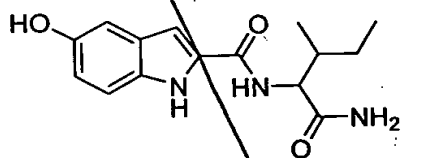
wherein R₁ is H or OH, R₂ is H or OH, R₃ is OH or H, and R₄ is CH₃, CH₂(CH₃)R, or CH₂(CH₃)S, R₅ is OCH₃, H, or OH, R₆ is OCH₃, F, H, or OH, and R₇ is OCH₃, H, OH, CO₂H, CO₂CH₃, CH₂CO₂H, or CH₂CO₂CH₃.

65. The method according to claim 63, wherein the compound has the following formula:



wherein R1 is OH or H, R2 is OH or H, R3 is OH or H, R4 is OH or H, R5 is OH, OMe, or H, R6 is OH, OMe, or H, R7 is OH, OMe, or H, and X is 0 or 1.

66. The method according to claim 63, wherein the compound has the following formula:



67. The method according to claim 50, wherein the protein kinase is a protein serine kinase.

68. The method according to claim 67, wherein the protein serine kinase is selected from the group consisting of MAP kinase, protein kinase C, and CDK kinase.

69. The method according to claim 50, wherein the compound further comprises one or more specificity side chain elements attached to the combination of the first and second modules.

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